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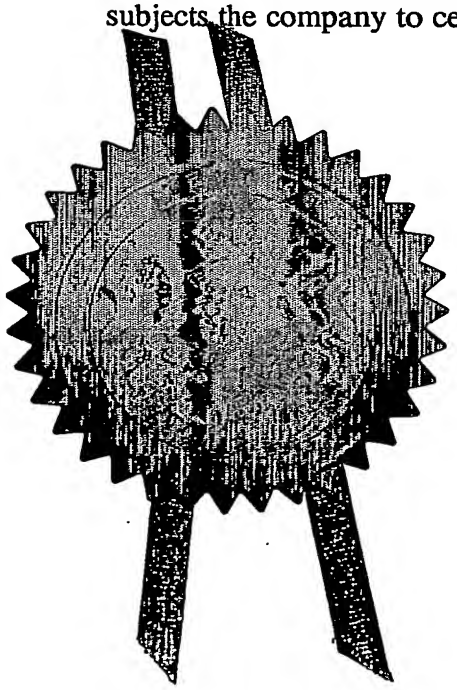

Signed

Dated 18 October 2004

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Patents Form 1/77

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P01/7700 0.00-0326967.7

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1/77

PATENT OFFICE
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19 NOV 2003
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## Request for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

The Patent Office

Cardiff Road
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NP10 8QQ

1. Your Reference — MM/PB60521P

2. Patent application number *(The Patent office will fill in this part)* — 0326967.7 — 19 NOV 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

Patents ADP number *(if you know it)* 07358700 3

If the applicant is a corporate body, give the country/state of its corporation — GB

4 Title of the invention — USE OF PYRIMIDINE DERIVATIVES FOR THE TREATMENT OF PSYCHIATRIC DISORDERS

5 Name of your agent *(if you know one)* — PETER DOLTON

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GLAXOSMITHKLINE
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TW8 9GS, GB

Patents ADP number *(if you know it)* 8072555006

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months

| Country | Priority application number *(if you know it)* | Date of Filing (day / month / year) |
|---|---|---|
| | | |

7. Divisionals: etc Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

| Number of earlier application | Date of filing (day / month / year) |
|---|---|
| | |

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? — YES

*Answer YES if:*

*a) any applicant named in part 3 is not an inventor, or*

*b) there is an inventor who is not named as an applicant, or*

*c) any named applicant is a corporate body*

*Otherwise answer NO See note (d)*

**Patents Form 1/77**

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

| | |
|---|---|
| Continuation sheets of this form | - |
| Description | 27 |
| Claim(s) | 4 |
| Abstract | 1 |
| Drawing(s) | - |

10. If you are also filing any of the following, state how many against each item

| | |
|---|---|
| Priority Documents | |
| Translations of priority documents | |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | |
| Request for preliminary examination and search *(Patent Form 9/77)* | |
| Request for substantive examination *(Patent Form 10/77)* | |
| Any other documents *(please specify)* | |

11. **I/We request the grant of a patent on the basis of this application**

**Signature** **PETER DOLTON.** **Date 19 November 2003**
***AGENT FOR THE APPLICANTS***

12. Name and daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

**Jean Harney +44 (0)208 047 4420**
**jean.l.harney@gsk.com**

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**Notes**

*a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.*

*b) Write your answers in capital letters using black ink or you may type them.*

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*d) If you have answered "Yes" in part 8, a Patents Form 7/77 will need to be filed.*

*e) Once you have filled in the form you must remember to sign and date it.*

*f) Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.*

PB60521P

# USE OF PYRIMIDINE DERIVATIVES FOR THE TREATMENT OF PSYCHIATRIC DISORDERS

The invention concerns the use of pyrimidine derivatives, which are COX-2 (cyclooxygenase-2) inhibitors, for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychoses and schizoaffective psychoses, temporary acute psychotic disorders; or in the treatment or prevention of major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders.

Moreover, the invention is concerned with the use of a pyrimidine derivative of the present invention in combination with a neuroleptic drug or an antidepressant for the treatment of the above mentioned psychiatric disorders.

The pyrimidine derivatives of the present invention have been already object of an International Patent Application WO 02/096885 by the same Applicant of the present invention, as COX-2 (cyclooxygenase-2) inhibitors. There is no disclosure in this applications of the use of the pyrimidine derivatives for the treatment of psychiatric disorders as defined above.

Moreover, the invention is concerned with the use of a COX-2 inhibitor in combination with a neuroleptic drug or an antidepressant for the treatment of psychiatric disorders such as those defined above.

Recently an International Patent Application WO 02/1002297 was published on 27 December 2002, disclosing the use of celecoxib in combination with risperidone for the treatment of schizophrenia.

The invention discloses the use of a COX-2 inhibitor for the treatment of psychiatric disorders, e.g. schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychoses and schizoaffective psychoses, temporary acute psychotic disorders, depressive episodes, recurring depressive episodes, manic episodes and bipolar affective disorders. Moreover, the invention discloses the use of a COX-2 inhibitor, in particular celecoxib, in combination with a neuroleptic drug, in particular risperidone, or an antidepressant, for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders.

The above-mentioned patent application discloses a long list of COX-2 inhibitors, see for example from page 6 to page 36, not including the compounds object of the present invention.

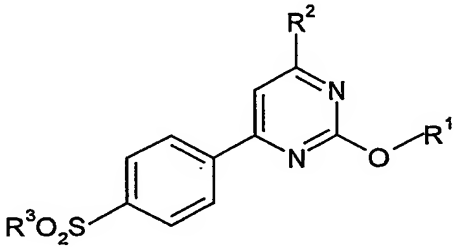
The preferred compounds are celecoxib, parecoxib, valdecoxib, etoricoxib and rofecoxib. A patient study is reported using celecoxib and risperidone.

An article was then published by the same authors on Am. J. Psychiatry, vol 159, June 2002, entitled, "Beneficial antypsychotic effects of Celecoxib add-on therapy compared to risperidone alone in schizophrenia". On page 1032 of the above article, the authors discussed a still open problem to be solved, i.e.;
"Several factors that may play a role in the effect of celecoxib in schizofrenia could not be considered because research and experience are lacking. First, with regard to the dose of celecoxib, the therapeutic raccomandations vary between 100 and 200 mg/day in the treatment of rheumatoid arthritis and 800 mg /day in familial polyposis. Since we know of no data for celecoxib treatment of CNS disorders, we chose a medium dose. Lower or higher doses may have been more beneficial".

Therefore, a need exists for further medicaments for the treatment of psychiatric disorders as above defined, wherein the COX-2 inhibitor can be administered in a much reduced dose, whilst retaining the desired clinical efficacy.

It is then possible to solve the above problem by using the compounds of the present invention.

The present invention is directed to the use of COX-2 inhibitors of general formula (I)



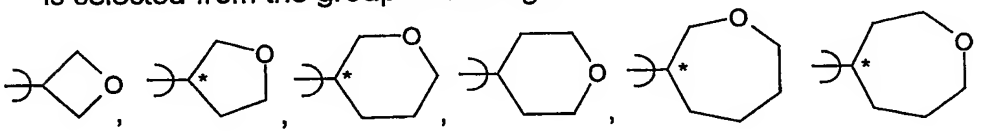
(I)

in which:

- $R^1$ is selected from the group consisting of H, $C_{1-6}$alkyl, $C_{1-2}$alkyl substituted by one to five fluorine atoms, $C_{3-6}$alkenyl, $C_{3-6}$alkynyl, $C_{3-10}$cycloalkyl$C_{0-6}$alkyl, $C_{4-12}$bridged cycloalkyl, $A(CR^4R^5)_n$ and $B(CR^4R^5)_n$;
- $R^2$ is $C_{1-2}$alkyl substituted by one to five fluorine atoms;
- $R^3$ is selected from the group consisting of $C_{1-6}$alkyl, $NH_2$ and $R^7CONH$;
- $R^4$ and $R^5$ are independently selected from H or $C_{1-6}$alkyl;
- A is an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more $R^6$;

$R^6$ is selected from the group consisting of halogen, $C_{1-6}$alkyl, $C_{1-6}$alkyl substituted by one more fluorine atoms, $C_{1-6}$alkoxy, $C_{1-6}$alkoxy substituted by one or more F, $NH_2SO_2$ and $C_{1-6}$alkyl$SO_2$;

B is selected from the group consisting of



where ) defines the point of attachment of the ring;

$R^7$ is selected from the group consisting of H, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, $C_{1-6}$alkyl$OC_{1-6}$alkyl, phenyl, $HO_2CC_{1-6}$alkyl, $C_{1-6}$alkyl$OCOC_{1-6}$alkyl, $C_{1-6}$alkyl$OCO$, $H_2NC_{1-6}$alkyl, $C_{1-6}$alkyl$OCONHC_{1-6}$alkyl and $C_{1-6}$alkyl$CONHC_{1-6}$alkyl; and

n is 0 to 4;

for the manufacture of a medicament for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychoses and schizoaffective psychoses, temporary acute psychotic disorders; or in the treatment or prevention of major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders.

Other mood disorders encompassed within the term major depressive disorders include dysthymic disorder with early or late onset and with or without atypical features, neurotic depression, post traumatic stress disorders, post operative stress and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

Compounds of the invention may be also useful in the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy, and circadian rhythmic disorders.

Compounds of the invention may be also useful in the treatment of tolerance to and dependence on a number of substances. For example, they are useful in the treatment of dependence on nicotine, alcohol, caffeine, phencyclidine (phencyclidine like compounds), or in the treatment of tolerance to and dependence on opiates (e.g. cannabis, heroin, morphine) or benzodiazepines; in the treatment of cocaine, sedative ipnotic, amphetamine

or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) addiction or a combination thereof.

Use of compounds of formula (I) allows use of much reduced amounts of COX-2 active, thus reducing the possibility of unwanted side-effects and simplifying administration of the drug.

Typically, a pharmaceutical acceptable salt may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

Suitable addition salts are formed from acids which form non-toxic salts and examples are hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, malate, fumarate, lactate, tartrate, citrate, formate, gluconate, succinate, piruvate, oxalate, oxaloacetate, trifluoroacetate, saccharate, benzoate, methansulphonate, ethanesulphonate, benzenesulphonate, p-toluensulphonate, , methanesulphonic, ethanesulphonic, p-toluenesulphonic, and isethionate.

In addition, prodrugs are also included within the context of this invention.
As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130, each of which are incorporated herein by reference.

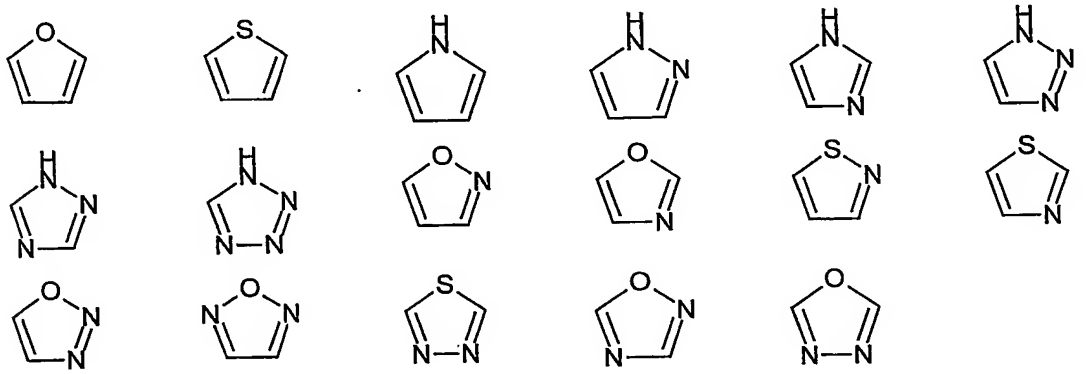
Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or in vivo, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy, amine or sulfhydryl groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol, sulfhydryl and amine functional groups of the compounds of structure (I).

With regard to stereoisomers, the compounds of structure (I) may have one or more asymmetric carbon atom and may occur as recemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

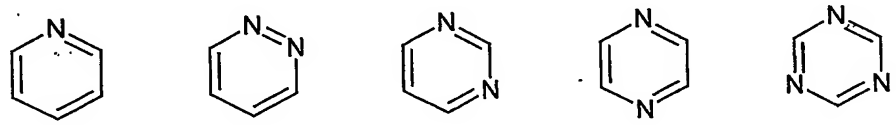
The term halogen is used to represent fluorine, chlorine, bromine or iodine.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

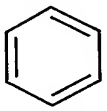
The term 5-membered heteroaryl means a heteroaryl selected from the following:



The term 6- membered heteroaryl means a heteroaryl selected from the following:



The term 6-membered aryl means:



It is to be understood that the present invention encompasses all isomers of the compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). In particular when the ring B lacks a plane of symmetry the compounds of formula (I) contain a chiral centre as indicated therein by the asterisk *. Furthermore, it will be appreciated by those skilled in the art that when $R^4$ and $R^5$ in formula (I) are different the corresponding compounds contain at least one chiral centre, by virtue of the asymmetric carbon atom defined thereby, and that such compounds exist in the form of a pair of optical isomers (i.e. enantiomers).

In one aspect of the invention $R^1$ is selected from the group consisting of H, $C_{1-6}$alkyl, $C_{1-2}$alkyl substituted by one to five fluorine atoms, $C_{3-6}$alkenyl, $C_{3-6}$alkynyl, $C_{3-10}$cycloalkyl$C_{0-6}$alkyl, $C_{4-12}$bridged cycloalkyl and $B(CR^4R^5)_n$.

In another aspect of the invention $R^1$ is $C_{1-6}$alkyl or $C_{1-2}$alkyl substituted by one to five fluorine atoms. In another aspect $R^1$ is $C_{2-6}$alkyl (e.g. n-butyl).

In another aspect of the invention $R^1$ is $C_{3-10}$cycloalkyl$C_{0-6}$alkyl, such as $C_{3-10}$cycloalkyl (e.g. cyclopentyl or cyclohexyl). In another aspect $R^1$ is $C_{3-10}$cycloalkylmethyl, such as $C_{3-7}$cycloalkylmethyl (e.g. cyclopentylmethyl).

In another aspect of the invention $R^1$ is $A(CR^4R^5)_n$.

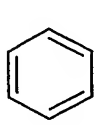
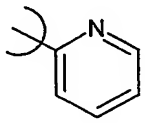
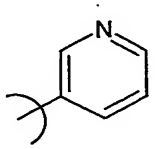
In another aspect of the invention $R^2$ is $CHF_2$, $CH_2F$ or $CF_3$. In another aspect $R^2$ is $CF_3$.

In another aspect of the invention $R^3$ is $C_{1-6}$alkyl, such as $C_{1-3}$alkyl (e.g. methyl).

In another aspect of the invention $R^4$ and $R^5$ are independently selected from H or methyl.

In another aspect $R^4$ and $R^5$ are both H.

In another aspect of the invention A is selected from the group consisting of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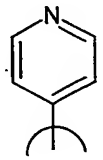

where

) defines the point of attachment of the ring

and A is unsubstituted or substituted by one or two $R^6$.

In another aspect of the invention $R^6$ is selected from the group consisting of halogen (e.g. F), $C_{1-3}$alkyl (e.g. methyl), $C_{1-3}$alkyl substituted by one to three fluorine atoms (e.g. $CF_3$), and $C_{1-3}$alkoxy (e.g. methoxy).

In another aspect of the invention $R^7$ is selected from the group consisting of $C_{1-6}$alkyl (e.g. ethyl), phenyl and aminomethyl.

In another aspect of the invention n is 1 to 4.

In another aspect of the invention n is 0 to 2 (e.g. 0).

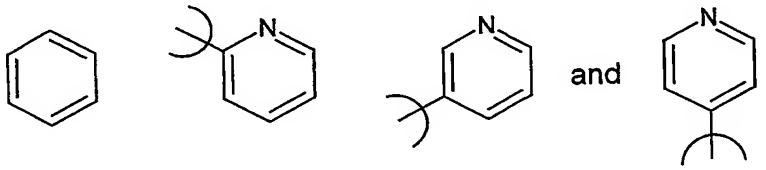
It is to be understood that the invention covers all combinations of particular aspects of the invention as described hereinabove.

Within the invention there is provided one group of compounds of formula (I) (group A) wherein: $R^1$ is $C_{1-6}$alkyl (e.g. n-butyl); $R^2$ is $CF_3$; and $R^3$ is $C_{1-6}$alkyl, such as $C_{1-3}$alkyl (e.g. methyl).

Within the invention there is provided another group of compounds of formula (I) (group B) wherein: $R^1$ is $C_{3-10}$cycloalkyl$C_{0-6}$alkyl, such as $C_{3-10}$cycloalkyl (e.g. cyclopentyl or cyclohexyl); $R^2$ is $CF_3$; and $R^3$ is $C_{1-6}$alkyl, such as $C_{1-3}$alkyl (e.g. methyl).

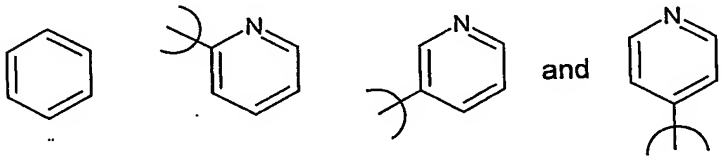
Within the invention there is provided another group of compounds of formula (I) (group C) wherein: $R^1$ is $C_{3-10}$cycloalkylmethyl, such as $C_{3-7}$cycloalkylmethyl (e.g. cyclopentylmethyl); $R^2$ is $CF_3$; and $R^3$ is $C_{1-6}$alkyl, such as $C_{1-3}$alkyl (e.g. methyl).

Within the invention there is provided another group of compounds of formula (I) (group D) wherein: $R^1$ is $A(CR^4R^5)_n$; $R^2$ is $CF_3$; $R^3$ is $C_{1-6}$alkyl, such as $C_{1-3}$alkyl (e.g. methyl); $R^4$ and $R^5$ are independently selected from H or methyl; A is selected from the group consisting of




and A is unsubstituted or substituted by one or two $R^6$; $R^6$ is selected from the group consisting of halogen (e.g. F), $C_{1-3}$alkyl (e.g. methyl), $C_{1-3}$alkyl substituted by one to three fluorine atoms (e.g. $CF_3$), and $C_{1-3}$alkoxy (e.g. methoxy); and n is 0 to 2 (e.g. 0).

Within group D, there is provided a further group of compounds (group D1) wherein: $R^1$ is $A(CR^4R^5)_n$; $R^2$ is $CF_3$; $R^3$ is methyl; $R^4$ and $R^5$ are both H; A is selected from the group consisting of




and A is unsubstituted or substituted by one or two $R^6$; $R^6$ is selected from the group consisting of fluorine, chlorine, methyl, $CF_3$ and methoxy; and n is 0 or 1.

In a preferred aspect the invention provides the following compounds:
2-(4-fluorophenoxy)-4-[4-(methylsulfonyl)phenyl]-6](trifluoromethyl)pyrimidine;
2-(4-methoxyphenoxy)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl)pyrimidine;
2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine;
2-[(5-chloropyridin-3-yl)oxy]-4-[4-(methylsulfony)phenyl]-6-(trifluoromethyl)pyrimidine;
2-(cyclohexyloxy)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine.
In a more preferred aspect the invention provides the following compound:
2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine.

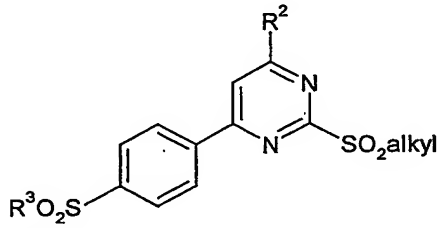
Since the compounds of the present invention, in particular compounds of formula (I), are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compound of formula (I) may be used for preparing the more pure forms used in pharmaceutical compositions. Although the purity of intermediate

compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are available in crystalline form.

When some of the compounds of this invention are allowed to crystallise or are recrysallised from organic solvents, solvent of recrystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all the polymorphic forms of the compounds of formula (I).

Compounds of formula (I) may be prepared by any method known in the art for the preparation of compounds of analogous structure.

Compounds of formula (I) may be prepared by a process which comprises:
reacting an alcohol $R^1OH$ of formula (II) or a protected derivative thereof with a compound of formula (III)




(III)

and thereafter and if necessary,
interconverting a compound of formula (I) into another compound of formula (I); and/or
deprotecting a protected derivative of compound of formula (I).

The overall synthesis of a compound of formula (I) is shown in Scheme 1 below in which, $R^1$ and $R^2$ are as defined in formula (I) above unless otherwise stated, $R^3$ is $C_{1-6}$alkyl; THF is tetrahydrofuran; MTBE is methyl t-butyl ether; and alkyl is a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group. Referring to Scheme 1, the preparation of compounds of formula (I) may conveniently be achieved by the treatment of compounds of formula (III) with an alcohol of formula (II) in the presence of sodium hydride. The reaction is conveniently carried out in a solvent such as THF and at between ambient temperature and reflux.

Conveniently the oxidation shown in Scheme 1 is effected using a monopersulfate compound, such as potassium peroxymonosulfate (known as Oxone™) and the reaction

is carried out in a solvent, such as an aqueous alcohol, (e.g. aqueous methanol), and at between -78°C and ambient temperature.

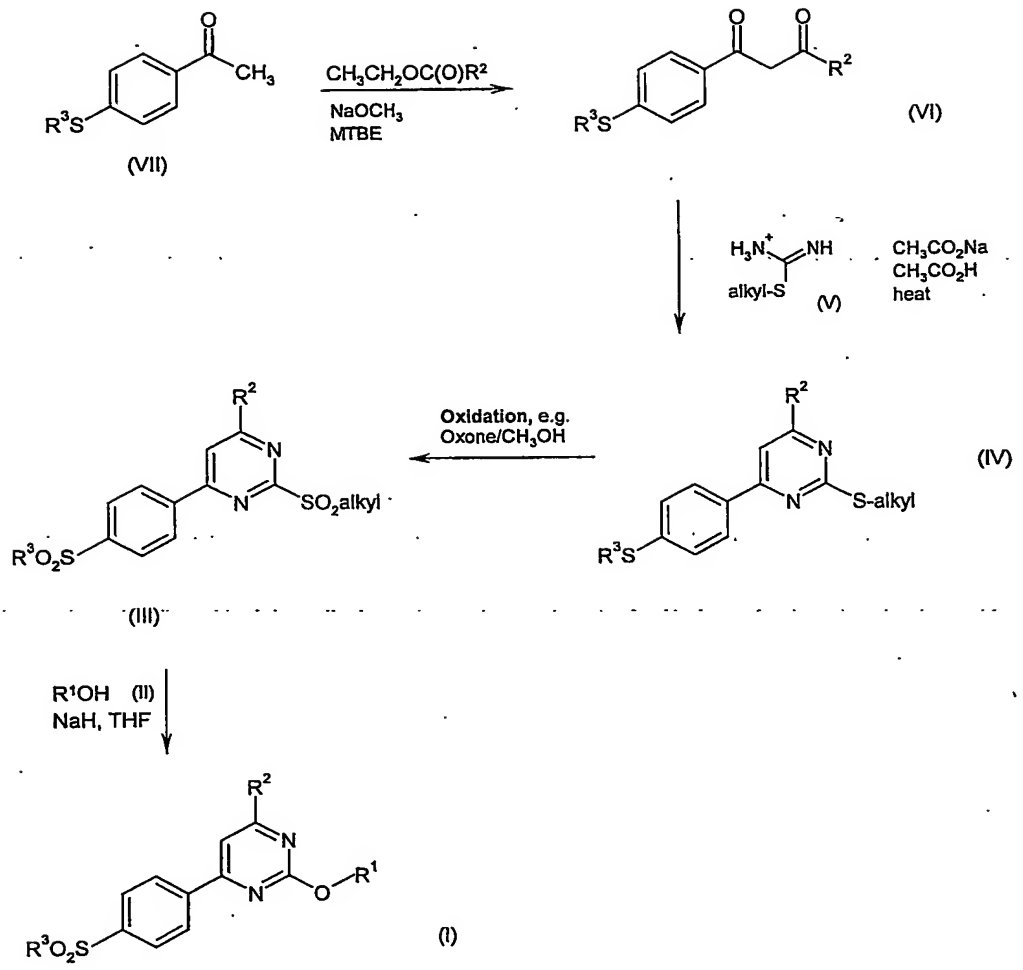
Alternatively, the oxidation shown in Scheme 1 may be effected using hydrogen peroxide in the presence of catalytic sodium tungstate dihydrate. The reaction may be carried out in a solvent such as acetic acid and at between ambient temperature and reflux (e.g. 50°C).

Referring to Scheme 1, the cyclisation of diones of formula (VI) to give the corresponding pyrimidines of formula (IV) is conveniently carried out employing a thioronium salt such as a 2-methyl-2-thiopseudourea sulfate and under reflux.

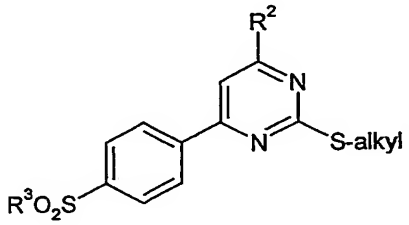
It will be appreciated by those skilled in the art that certain of the procedures described in Scheme 1 for the preparation of compounds of formula (I) or intermediates thereto may not be applicable to some of the possible substituents.

It will be further appreciated by those skilled in the art that it may be necessary or desirable to carry out the transformations described in Scheme 1 in a different order from that described, or to modify one or more of the transformations, to provide the desired compound of formula (I).

Scheme 1




In one variation of Scheme 1, compounds of formula (III) wherein $R^3$ is $C_{1-6}$alkyl or $NH_2$ may be prepared by oxidising a compound of formula (IV)A:



(IV)A

under oxidation conditions described hereinabove. Compounds of formula (IV)A may be prepared according to the general procedures of Scheme 1 by employing sulphonyl derivatives in place of the corresponding sulfide compounds of formulae (VI) and (VII).

It will be appreciated by those skilled in the art that compounds of formula (I) may be prepared by interconversion, utilising other compounds of formula (I) as precursors. Suitable interconversions, such as alkylations, are well known to those skilled in the art and are described in many standard organic chemistry texts, such as 'Advanced Organic Chemistry' by Jerry March, fourth edition (Wiley, 1992), incorporated herein by reference. For example, compounds of formula (I) wherein $R^1$ is $C_{1-6}$alkyl, $C_{1-2}$alkyl substituted by one

to five fluorine atoms, $C_{3-6}$alkenyl, $C_{3-6}$alkynyl, $C_{3-10}$cycloalkyl$C_{0-6}$alkyl, $C_{4-12}$bridged cycloalkane, $A(CR^4R^5)_n$ (with the proviso that n is not zero) and $B(CR^4R^5)_n$ may be prepared by alkylating the corresponding compound of formula (I) wherein $R^1$ is H.

Acylation of compounds of formula (I) wherein $R^3$ is $NH_2$, to provide compounds of formula (I) wherein $R^3$ is $R^7CONH$, may be carried out by conventional means, for example by employing conventional acylating agents such as those described in 'Advanced Organic Chemistry', pp 417-424, incorporated herein by reference.

As will be appreciated by those skilled in the art it may be necessary or desirable at any stage in the synthesis of compounds of formula (I) to protect one or more sensitive groups in the molecule so as to prevent undesirable side reactions. The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W. Green and Peter G M Wuts, second edition, (John Wiley and Sons, 1991), incorporated herein by reference, which also describes methods for the removal of such groups.

Alcohols of formula (II) are either known compounds or may be prepared by literature methods, such as those described in 'Comprehensive Organic Transformations: a guide to functional group preparations' by Richard Larock (VCH, 1989), incorporated herein by reference.

Thioronium salts of formula (V) are either known compounds or may be prepared by literature methods, such as those described in A H Owens *et al*, Eur J Med Chem, 1988, 23(3), 295-300, incorporated herein by reference.

Acetophenones of formula (VII) are either known compounds or may be prepared by conventional chemistry.
Certain intermediates described above are novel compounds, and it is to be understood that all novel intermediates herein form further aspects of the present invention.

Compounds of formulae (III) and (IV) are key intermediates and represent a particular aspect of the present invention.

Solvates (e.g. hydrates) of a compound of the invention may be formed during the work-up procedure of one of the aforementioned process steps.

Conveniently, compounds of the invention are isolated following work-up in the form of the free base. Pharmaceutically acceptable acid addition salts of the compounds of the invention may be prepared using conventional means.

In the context of the present invention a treatment of a disease or disorder is meant to cover the actual therapy as well as maintenance therapy and prophylaxis against recurrence.

Furthermore, the invention concerns the use of COX-2 inhibitors of formula (I) in combination with neuroleptics or antidepressants for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychoses and schizoaffective psychoses, temporary acute psychotic disorders; or in the treatment or prevention of major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders.

The invention is also directed to a novel kit-of-parts that is suitable for use in the treatment of psychiatric disorders as above defined, the kit comprising a first dosage form comprising a neuroleptic or an antidepressant and a second dosage form comprising a COX-2 inhibitor, for simultaneous, separate or sequential administration.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

As stated above, the compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

A proposed daily dosage of a compound of formula (I) for the treatment of man is 0.01mg/kg to 500mg/kg, such as 0.05mg/kg to 100mg/kg, e.g. 0.1mg/kg to 50mg/kg, which may be conveniently administered in 1 to 4 doses. The precise dose employed will depend on the age and condition of the patient and on the route of administration. Thus, for example, a daily dose of 0.25mg/kg to 10mg/kg may be suitable for systemic administration.

Preferably, compounds of formula (I) are used in the form of tablets for oral administration.

According to a further embodiment of the present invention, the COX-2 inhibitor of the present invention is used in combination with a neuroleptic drug or an antidepressant for the manufacture of a medicament for the treatment of psychiatric disorders as defined above.

Combinations can also include a mixture of one or more COX-2 inhibitors of the present invention or a mixture of one COX-2 inhibitor of the present invention with another, for example, available on the market (Celebrex®, Vioox®) or generally known as COX-2 inhibitor with one or more neuroleptic agents or antidepressants, mood stabilisers or antimanic.

In particular, the combination of a COX-2 inhibitor with a neuroleptic drug is useful for the treatment of schizophrenia, whereas the combination of a COX-2 inhibitor with an

antidepressant is applicable for the treatment of depressive disorders. Especially, the combination of a COX-2 inhibitor with an antimanic agent, a mood stabiliser or an antidepressant for bipolar depression.

Both classical and atypical neuroleptics can be used for the add-on use according to the invention, atypical neuroleptics being preferred.

Examples of neuroleptic drugs that are useful in the present invention include, but are not limited to: butyrophenones, such as haloperidol, pimozide, and droperidol; phenothiazines, such as chlorpromazine, thioridazine, mesoridazine, trifluoperazine, perphenazine, fluphenazine, thiflupromazine, prochlorperazine, and acetophenazine; thioxanthenes, such as thiothixene and chlorprothixene ; thienobenzodiazepines; dibenzodiazepines; benzisoxazoles; dibenzothiazepines; imidazolidinones ; benziso-thiazolyl-piperazines; triazine such as lamotrigine; dibenzoxazepines, such as loxapine; dihydroindolones, such as molindone; aripiprazole; and derivatives thereof that have antipsychotic activity.

Examples of neuroleptic drugs that are preferred for use in the present invention are shown in Table 1.

Table 1
Neuroleptic drugs

| Common Name | Trade Name | Route of Administration | Form | Dosage Range and (Median)[a] |
|---|---|---|---|---|
| Clozapine | CLOZARIL | oral | tablets | 12.5-900 mg/day (300-900 mg/day) |
| Olanzapine | ZYPREXA | oral | tablets | 5-25 mg/day (10-25 mg/day) |
| Ziprasidone | GEODON | oral | capsules | 20-80mg/twice a day (80-160 mg/day) |
| Risperidone | RISPERDAL | oral | solution tablets | 2-16 mg/day tablets (4-12 mg/day) |
| Quetiapine fumarate | SEROQUEL | oral | tablets | 50-900 mg/day (300-900 mg/day) |

| | | | | |
|---|---|---|---|---|
| Sertindole | SERLECT | | | (4-24 mg/day) |
| Amisulpride | | | | |
| Haloperidol | HALDOL | oral | tablets | 1-100 mg/day (1-15 mg/day) |
| Haloperidol Decanoate | HALDOL Decanoate | parenteral | injection | |
| Haloperidol lactate | HALDOL INTENSOL | oral | solution | |
| | | parenteral | injection | |
| Chlorpromazine | THORAZINE | rectal | suppositories | 30-800 mg/day (200-500 mg/day) |
| | | oral | capsules solution tablets | |
| | | parenteral | injection | |
| Fluphenazine | PROLIXIN | | | 0.5-40 mg/day (1-5 mg/day) |
| Fluphenazine decanoate | PROLIXIN Decanoate | parenteral | injection | (about one-half the dosage shown for oral) |
| Fluphenazine enanthate | PROLIXIN | parenteral | injection | (same as above |
| Fluphenazine hydrochloride | PROLIXIN | oral | elixer solution | |
| | | parenteral | injection | |
| Thiothixene | NAVANE | oral | capsules | 6-60 mg/day (8-30 mg/day) |
| Thiothixene hydrochloride | NAVANE | oral | solution | |
| | | parenteral | injection | |
| Trifluoperazine | STELAZINE | | | (2-40 mg/day) |
| Perphenazine | TRILAFON | oral | solution tablets | 12-64 mg/day (16-64 mg/day) |
| | | parenteral | injection | |
| Perpehazine and Amitriptyline hydrochloride | ETRAFON TRIAVIL | oral | tablets | |
| Thioridazine | MELLARIL | oral | suspension solution tablets | 150-800 mg/day (100-300 mg/day) |

| | | | | |
|---|---|---|---|---|
| Mesoridazine | | | | (30-400 mg/day) |
| Molindone | MOBAN | | | 50-225 mg/day (15-150 mg/day) |
| Molindone hydrochloride | MOBAN | oral | solution | |
| Loxapine | LOXITANE | | | 20-250 mg/day (60-100 mg/dav) |
| Loxapine hydrochloride | LOXITANE | oral<br>parenteral | solution<br>injection | |
| Loxapine succinate | LOXITANE | oral | capsules | |
| Pimozide | | | | (1-10 mg/day) |
| Flupenthixol | | | | |
| Promazine | SPARINE | | | |
| Triflupromazine | VESPRIN | | | |
| Chlorprothixene | TARACTAN | | | |
| Droperidol | INAPSINE | | | |
| Acetophenazine | TINDAL | | | |
| Prochlorperazine | COMPAZINE | | | |
| Methotrimeprazine | NOZINAN | | | |
| Pipotiazine | PIPOTRIL | | | |
| Aripiprazole | | | | |
| Hoperidone | | | | |

Examples of tradenames and suppliers of selected neuroleptic drugs are as follows : clozapine (available under the tradename CLOZARIL®, from Mylan, Zenith Goldline, UDL, Novartis); olanzapine (available under the tradename ZYPREX®, from Lilly ; ziprasidone (available under the tradename GEODON®, from Pfizer); risperidone (available under the tradename RISPERDAL®, from Janssen); quetiapine fumarate (available under the tradename SEROQUEL®, from AstraZeneca); haloperidol (available under the tradename HALDOL®, from Ortho-McNeil); chlorpromazine (available under the tradename THORAZINE®, from SmithKline Beecham (GSK); fluphenazine (available under the tradename PROLIXIN®, from Apothecon, Copley, Schering, Teva, and American Pharmaceutical Partners, Pasadena); thiothixene (available under the tradename NAVANE®;, from Pfizer); trifluoperazine (10-[3-(4-methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)phenothiazine dihydrochloride, available under the tradename STELAZINE®, from Smith Klein Beckman; perphenazine (available under the tradename TRILAFON®; from Schering); thioridazine (available under the tradename MELLARIL®;

from Novartis, Roxane, HiTech, Teva, and Alpharma) ; molindone (available under the tradename MOBAN®, from Endo); and loxapine (available under the tradename LOXITANE®; from Watson). Furthermore, benperidol (Glianimon®), perazine (Taxilan®) or melperone (Eunerpan®)) may be used.

Other preferred neuroleptic drugs include promazine (available under the tradename SPARINE®), triflurpromazine (available under the tradename VESPRIN®), chlorprothixene (available under the tradename TARACTAN®), droperidol (available under the tradename INAPSINE®), acetophenazine (available under the tradename TINDAL®;), prochlorperazine (available under the tradename COMPAZINE®), methotrimeprazine (available under the tradename NOZINAN®), pipotiazine (available under the tradename PIPOTRIL®), ziprasidone, and hoperidone.

Other preferred neuroleptic drugs include the compounds disclosed in the patent application GB0212404.4, filed by the same Applicant of the present invention. Among them the compound 7-[4-(4-chloro-benzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine and its pharmaceutically acceptable salts are particularly preferred.

Preferred neuroleptic drugs include risperidone and aripiprazole (from Bristol Myers Squibb Company, see e. g. Stahl SM; Dopamine-system stabilizers, aripiprazole and the next generation of antipsychotics, part 1,"goldilocks"-actions at dopamine receptors; J. Clin. Psychiatry 2001,62,11: 841-842).

The most preferred neuroleptic drug within the present invention is risperidone (Risperdal®;), its manufacture and pharmacological activity is described in EP 0 196 132. Risperidone acts as an antagonist to neurotransmitters, in particular dopamine, and is used for the treatment of psychoses.

Within the present invention, the neuroleptic risperidone can be administered at a dose of 2-6 mg/day, preferably 4-5 mg. The dose for compounds (I) may range from 0.25 mg/kg to 5 mg/kg, preferably 0.8 mg/kg to 3.0 mg/kg. Preferably, the administration occurs once daily.

Various types of antidepressants can be used for the add-on use according to the present invention. Examples of antidepressants that are useful in the present invention include, but are not limited to: tricyclic antidepressants such as amitriptyline (5-(3-dimethylamino propylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptен), amitriptyline oxide, desipramine (10,11-dihydro-5-(3-methylaminopropyl)-5H-dibenz[b,f]flazepin), dibenzepin (10-(2-dimethylaminoethyl)-5,11-dihydro-5-methyl11H-dibenzo[b,e][1,4]diazepin-11-on), dosulepin (3-(6H-dibenzo[b,e]thiepin-11-yliden)-N,N-dimethylpropylamine), doxepin (3-(6H-dibenzo[b,e]oxepin-11-yliden)-dimethylpropylamine), chloroimipramine, imipramine (5-(3-dimethylaminopropyl)-5,11-dihydro-5H-dibenz[b,f]azepin), nortriptyline (3-(10,11-

dihydro-5Hdibenzo[a,d]cyclohepten-5-yliden)-N-methyl-1-propaneamine), mianserin (1, 2, 3, 4, 10, 14b-hexahydro-2-methyl-dibenzo[c,f]pyrazino[1,2-a]azepin), maprotiline (N-methyl-9,10-ethanoanthracene-9(10H)-propaneamine), trimipramine (5-[3-dimethyl-amino)-2-methylpropyl]-10,11-dihydro-5H-dibenz[b,f]azepin) or viloxazine (RS)-2-(2--ethyoxyphenoxymethyl)-morpholine), modern antidepressants such as trazodone (2-{3-[4-(3-chlorophenyl)-1-piperazinyl]-propyl}-1,2,4-triazol[4,3a]pyridine-3(2H)-on, nefazodone (2-{3-[4-(3-chlorophenyl)-1-piperazinyl]propyl)-5-ethyl-2, 4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-on), mirtazapine ((±)-1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a] pyrido[2,3-c][2] benzazepin), venlafaxine ( ()-1-2- (dimethylamino)-1- (4-methoxyphenyl)-ethyl] cyclohexanol) or reboxetine ((±)-(2RS)-2-[(αSR)-α-(2-ethoxyphenoxy)benzyl] morpholine), inhibitors of monoaminooxidases such as tranylcypromine (trans-2-phenyl cyclopropylamine), brofaromine or moclobemide (4-chloro-N-(2-morpholinoethyl)-benzamide), selective inhibitors of serotonin-uptake such as citalopram, paroxetine, fluoxetine ((RS)-N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propylamine, available under the tradename PROZAC®)), fluvoxamine ((E)-5-methyoxy-4'-(trifluoromethyl)-valerophenon-O-(2-aminoethyl)oxime) or sertraline ((1S-cis)-(+)-4- (3,4-dichlorophenyl)-1, 2,3,4-tetrahydro-N-methyl-1-naphthalinamine), and vegetable antidepressants such as Hypericum (St. John's wort).

Selective antagonists of $NK_1$ receptor for use in the present invention include those generically and specifically disclosed in the following patent specifications whose disclosures are here incorporated by reference:
US Patent Specification Nos. 4839465, 5338845, 5594022, 6169097, 6197772, 6222038, 6204265, 6329392, 6316445, 2001039286, 2001034343, 2001029297, 2002193402, 2002147212, 2002147207, 2002143003 and 2002022624; and in European Patent Specification Nos. 284942, 327009, 333174, 336230, 360390, 394989, 428434, 429366, 436334, 443132, 446706, 482539, 484719, 499313, 512901, 512902, 514273, 514275, 517589, 520555, 522808, 525360, 528495, 532456, 533280, 577394, 591040, 615751, 684257, 1176144, 1110958, 1176144, 1172106, 1103545, and 1256578; and in International Patent Application Nos. 90/05525, 90/05729, 91/02745, 91/12266, 91/18016, 91/18899, 92/01688, 92/06079, 92/15585, 92/17449, 92/20676, 92/21677, 92/22569, 93/00331, 93/01159, 93/01160, 93/01165, 93/01169, 93/01170, 94/01402, 94/26735, 95/06645, 95/08549, 95/14017, 95/16679, 95/18124, 95/23798, 95/28389, 95/33744, 96/05181, 96/18643, 96/21661, 96/29326, 96/32386, 96/34857, 96/37489, 97/02824, 97/05110, 97/08166, 97/13514, 97/14671, 97/16440, 97/17362, 97/19074, 97/19084, 97/19942, 97/21702, 97/22597, 97/22604, 97/23455, 97/24324, 97/24350, 97/25322, 97/25988, 97/27185, 97/30989, 97/30990, 97/30991, 97/32865, 97/38692, 97/44035, 97/49393, 97/49710, 98/02158, 98/04561, 98/07694, 98/07722, 98/08826, 98/13369, 98/17276, 98/18761, 98/18785, 98/18788, 98/20010, 98/24438, 98/24439, 98/24440, 98/24441, 98/24442, 98/24442, 98/24443, 98/24444, 98/24445, 98/24446, 98/24447, 98/28297, 98/43639, 98/45262, 98/49170, 98/54187, 98/57954, 98/57972, 99/00388, 99/01444, 99/01451, 99/07677, 99/07681, 99/09987, 99/21823, 99/24423, 99/25364, 99/26924, 99/27938, 99/36424, 99/52903, 99/59583, 99/59972, 99/62893, 99/62900,

99/64000, 00/02859, 00/06544, 00/06571, 00/06572, 00/06578, 00/06580, 00/15621, 00/20003, 00/21512, 00/21564, 00/23061, 00/23062, 00/23066, 00/23072, 00/20389, 00/25745, 00/26214, 00/26215, 00/34243, 00/34274, 00/39114, 00/47562, 01/77069, 01/25233, 01/30348, 01/87866, 01/94346, 01/90083, 01/87838, 01/85732, 01/77100, 01/77089, 01/77069, 01/46176, 01/46167, 01/44200, 01/32625, 01/29027, 01/25219, 02/32865, 02/00631, 02/81461, 02/92604, 02/38575, 02/57250, 02/22574, 02/74771, 02/26710, 02/28853, 02/102372, 02/85458, 02/81457, 02/74771, 02/62784, 02/60898, 02/60875, 02/51848, 02/51807, 02/42280, 02/34699, 02/32867, 02/32866, 02/26724, 02/24673, 02/24629, 02/18346, 02/16344, 02/16343, 02/16324, 02/12168, 02/08232 and 02/06236; and in British Patent Specification Nos. 2216529, 2266529, 2268931, 2269170, 2269590, 2271774, 2292144, 2293168, 2293169 and 2302689; and in Japanese Patent Specification No 6040995. Preferably, a particularly useful class of NK1 receptor antagonists for use in the combinations of the present invention is represented by those compounds described in WO 01/25219. More preferably the compound 2-(S)-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate is used.

Selective antagonists of CRF-1 receptor for use in the present invention include those generically and specifically disclosed in the following patent specifications whose disclosures are here incorporated by reference:
US Patent Specification Nos.: 4,605,642, 5,063,245, 6,348,466, 6,348,466 and in International Patent Application Nos. 94/13676, 94/13677, 95/10506, 95/33727, 95/33750, 95/34563, 96/35689, 96/39400, 97/00868, 97/14684, 97/29109, 97/29110, 97/35580, 97/35846, 97/44038, 98/03510, 98/05661, 98/08821, 98/08846, 98/08847, 98/11075, 98/15543, 98/21200, 98/27066, 98/29397, 98/29413, 98/35967, 98/42699, 98/45295, 98/47874, 98/47903, 99/01454, 99/01439, 99/00373, 99/10350, 99/12908, 99/38868, 00/27846, 00/27850, 01/44207, 02/87573, 02/08895, 02/100863, 02/094826, 03/008412, 03/008414 and in European patent publications: 778277, 773023, 576350, 112909.

Other preferred antidepressant drugs are disclosed in WO99/37305 and among them, (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, is preferred.

The invention is also directed to a novel kit-of-parts that is suitable for use in the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, comprising a first dosage form comprising a neuroleptic agent or an antidepressant and a second dosage form comprising the COX-2 inhibitor as defined in the present invention or prodrug thereof, for simultaneous, separate or sequential administration.

According to a preferred embodiment, the dosage form comprising a neuroleptic agent or an antidepressant and the second dosage form comprising the COX-2 inhibitor as defined in the present invention are administered simultaneously.

The subject pharmaceutical kit-of-parts may be administered enterally (orally) or parenterally. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric coated capsules, and syrups. Preferably the administration of a pharmaceutical kit comprising the COX-2 inhibitor as defined in the present invention and a neuroleptic or antidepressant occurs enterally (orally), in form of tablets.

The treatment of psychiatric disorders with the COX-2 inhibitor as defined in the present invention, alone or in combination with a neuroleptic or antidepressant, may occur in addition to further drug therapies.

Thus, tranquilizers may be used for the treatment of agitation, anxiety or sleep disturbances. Preferably lorazepam is used, which belongs to the class of benzodiazepines.

EXPERIMENTAL PART

The Intermediates and Examples that follow illustrate the invention but do not limit the invention in any way. All temperatures are in $^{0}C$. Flash column chromatography was carried out using Merck 9385 silica. Solid Phase Extraction (SPE) chromatography was carried out using Varian Mega Bond Elut (Si) cartridges (Anachem) under 15mmHg vacuum. Thin layer chromatography (Tlc) was carried out on silica plates. In addition to those already defined, the following abbreviations are used: Me, methyl; Ac, acyl; DMSO, dimethylsulphoxide; TFA, trifluoroacetic acid; DME, dimethoxyethane; DCM, dichloromethane; NMP, N-methyl pyrrolidone; and MTBE, methyl t-butyl ether.

Intermediate 1

4,4,4-Trifluoro-1-[4-(methylthio)phenyl]butane-1,3-dione

To a solution of ethyl trifluoroacetate (7.95ml, 1.1eq) in MTBE (125ml) was added dropwise 25% sodium methoxide in methanol (16ml, 1.2eq). 4-Methylthioacetophenone (Aldrich, 10g, 0.06mol) was added portionwise and the mixture stirred at ambient temperature overnight. 2N Hydrochloric acid (40ml) was added cautiously and the organic phase separated, washed with brine and dried ($Na_2SO_4$) to give an orange solid. The orange solid was recrystallised from hot isopropanol to give the title compound as a yellow crystalline solid (11.25g, 71%).

MH- 261

Intermediate 2

2-(Methylthio)-4-[4-(methylthio)phenyl]-6-(trifluoromethyl) pyrimidine

To a mixture of 4,4,4-trifluoro-1-[4-(methylthio)phenyl]butane-1,3-dione (5g) and 2-methyl-2-thiopseudourea sulfate (5.1g, 0.98eq) in acetic acid (100ml) was added sodium acetate (3g, 2eq) and heated under reflux for 8h. The mixture was concentrated *in vacuo* and

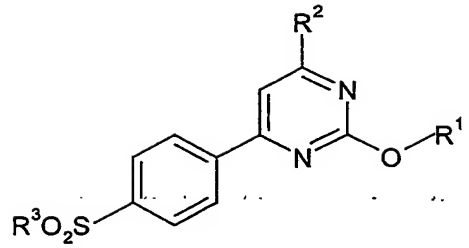
water (100ml) added to give a solid, which was isolated by filtration to give the title compound as a yellow solid (5.8g, quantitative).
MH+ 317

Intermediate 3
2-(Methylsulfonyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine
To a solution of 2-(methylthio)-4-[4-(methylthio)phenyl]-6-(trifluoromethyl) pyrimidine (5.78g) in MeOH (500ml) was added a solution of OXONE™ (Aldrich, 56.23g, 5eq) in water (200ml). The mixture was stirred at ambient temperature overnight, concentrated *in vacuo* and the residue partitioned between water and ethyl acetate (2 x 100ml). The combined organic phases were dried and concentrated *in vacuo* to an off-white solid which was triturated with hot isopropanol to give the title compound as a white solid (5.6g, 80%).
MH+ 381
Tlc $SiO_2$ Ethyl acetate:cyclohexane (1:1) Rf 0.45

Example 1
2-(4-Fluorophenoxy)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine.
To a stirred solution of 4-fluorophenol (37mg, 0.33mmole) in dry tetrahyrofuran (10ml) was added, under an atmosphere of nitrogen, sodium hydride (60% dispersion in oil, 13mg, 0.33mmole) and the resulting mixture stirred at 20 for 30min. To the stirred reaction mixture was added 2-(methylsulfonyl)-4[4-(methylsulfonyl)phenyl]-6-trifluoromethyl)pyrimidine (114mg, 0.33mmole) in a single portion, and stirring was continued for 2h. The solvent was evaporated, and the residue partitioned between dichloromethane and 2N sodium hydroxide. The dried organic phase was evaporated to dryness. The residue was purified on a silica gel SPE cartridge eluting with chloroform to afford the title compound as a colourless solid (99mg, 80%).
MH+ 413.

Examples 2 to 10
Examples 2 to 10, as shown in Table 1 that follows, were prepared in the manner described for Example 1.

**Table 1**



(I)

| Ex | $R^1$ | $R^2$ | $R^3$ | MS | |
|---|---|---|---|---|---|
| 2 | 3,4-difluorophenyl | $CF_3$ | $CH_3$ | MH+ | 431 |
| 3 | 4-methoxyphenyl | $CF_3$ | $CH_3$ | MH+ | 425 |
| 4 | 4-fluorobenzyl | $CF_3$ | $CH_3$ | MH+ | 427 |
| 5 | 4-bromophenyl | $CF_3$ | $CH_3$ | MH+ | 474 |
| 6 | 4-methylphenyl | $CF_3$ | $CH_3$ | MH+ | 409 |
| 7 | 5-chloropyridin-3-yl | $CF_3$ | $CH_3$ | MH+ | 431 |
| 8 | cyclohexyl | $CF_3$ | $CH_3$ | MH+ | 401 |
| 9 | cyclopentylmethyl | $CF_3$ | $CH_3$ | MH+ | 401 |
| 10 | n-butyl | $CF_3$ | $CH_3$ | MH+ | 375 |

Example 11

2-Butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine

Sodium methoxide (6.6kg of a 30%w/w solution in methanol) was added over at least 30min to a solution of 4-(methylthio)acetophenone (5.0kg) and methyl trifluoroacetate (4.25kg) in tert-butylmethylether (40L) at 40±3°C. The solution was heated at 40±3°C for at least 3h. Acetic acid (55L) was added, followed by S-methyl 2-thiopseudourea sulfate (5.45kg) and the mixture concentrated to *ca.* 45L. The mixture was heated at about 110°C for at least a further 8h (overnight) then acetic acid (20L) was added before cooling to 50±3°C. A solution of sodium tungstate dihydrate (0.2kg) in water (2.5L) was added, followed by hydrogen peroxide (20.7kg of 30%w/v solution), which was added over at least 3h, maintaining the temp at *ca.* 50°. The mixture is heated at *ca.* 50°C for at least 12h before cooling to 20±3°C. A solution of sodium sulphite (3.45kg) in water (28L) was then added over at least 30min whilst maintaining the temperature at 20±3°. The mixture was aged at 20±3°C for *ca.* 1h and 2-(methylsulfonyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine collected by filtration, washed with water (3x15L) and dried at up to 60° *in vacuo.* Yield, 9.96kg, 90% of theory.

A suspension of 2-(methylsulfonyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-pyrimidine (525g) in n-butanol (5.25L) was treated with potassium carbonate (210g) at 20±5°C. The mixture was heated to 50±5°C overnight until the reaction was complete by HPLC. Acetic acid (1.57L) was added dropwise, to control any gas evolution, keeping the temperature at 50±5°C. Water (3.67L) was then added over 30min keeping the temperature at 50±5°C to allow full crystallisation to occur. The slurry was then cooled to 20-25°C and aged for at least 1 hour. The resulting product was then filtered under vacuum and washed with a mixture of n-butanol (787mL), acetic acid (236mL), and water (551mL) followed by water (2x1.57L). The product was then dried at up to *ca*50°C under vacuum to yield the title compound. Yield, 457g, 88.4% of theory. The title compound was found to be identical to that of Example 10.

$^1$H NMR ($CDCl_3$) δ: 8.33(2H, d, para-di-substituted CH); 8.11(2H, d, para-di-substituted CH); 7.70(1H, s, aromatic CH); 4.54(2H, t, butyl $CH_2$); 3.12(3H, s, sulphone $CH_3$); 1.88(2H, m, butyl $CH_2$); 1.55(2H, m, butyl $CH_2$); 1.01(3H, t, butyl $CH_3$).

## Example 12
## Biological Data
## Cell Based Assay

Inhibitory activity against human COX-1 and COX-2 was assessed in COS cells which had been stably transfected with cDNA for human COX-1 and human COX-2. 24 Hours prior to experiment, COS cells were transferred from the 175cm$^2$ flasks in which they were grown, onto 24-well cell culture plates using the following procedure. The incubation medium (Dulbecco's modified eagles medium (DMEM) supplemented with heat-inactivated foetal calf serum (10%v/v), penicillin (100 IU/ml), streptomycin (100µg/ml) and geneticin (600µg/ml)) was removed from a flask of confluent cells (1 flask at confluency contains approximately 1x10$^7$ cells). 5ml of phosphate buffered saline (PBS) was added to the flask to wash the cells. Having discarded the PBS, cells were then incubated with 5ml trypsin for 5 minutes in an incubator (37°). The flask was then removed from the incubator and 5ml of fresh incubation medium was added. The contents of the flask was transferred to a 250ml sterile container and the volume of incubation medium subsequently made up to 100ml. 1ml cell suspension was pipetted into each well of 4x24-well cell culture plates. The plates were then placed in an incubator (37°C, 95% air/5% $CO_2$) overnight. If more than 1 flask of cells were required, the cells from the individual flasks were combined before being dispensed into the 24-well plates.

Following the overnight incubation, the incubation medium was completely removed from the 24-well cell culture plates and replaced with 250µl fresh DMEM (37°C). The test compounds were made up to 250x the required test concentration in DMSO and were added to the wells in a volume of 1µl. Plates were then mixed gently by swirling and then placed in an incubator for 1 hour (37°C, 95% air/5% $CO_2$). Following the incubation period, 10µl of arachidonic acid (750µM) was added to each well to give a final arachidonic acid concentration of 30µM. Plates were then incubated for a further 10 minutes, after which the incubation medium was removed from each well of the plates and

stored at -20°C, prior to determination of prostaglandin $E_2$ (PGE2) levels using enzyme immunoassay. The inhibitory potency of the test compound was expressed as an $IC_{50}$ value, which is defined as the concentration of the compound required to inhibit the PGE2 release from the cells by 50%. The selectivity ratio of inhibition of COX-1 versus COX-2 was calculated by comparing respective $IC_{50}$ values.

The following $IC_{50}$ values for inhibition of COX-2 and COX-1 were obtained from the cell based assay for compounds of the invention:

| Example No. | COX-2: $IC_{50}$(nM) | COX-1: $IC_{50}$(nM) |
|---|---|---|
| 1 | <1 | 81,300 |
| 2 | 23 | 9,675 |
| 3 | 4 | 2,923 |
| 5 | 6 | 61,380 |

Example 13

Microsomal Assay

Inhibitory activity against microsomal h-COX2 was assessed against a microsomal preparation from baculovirus infected SF9 cells. An aliquot of microsomal preparation was thawed slowly on ice and a 1/40,000 dilution prepared from it into the assay buffer (sterile water, degassed with argon containing 100mM HEPES (pH 7.4), 10mM EDTA (pH7.4), 1mM phenol, 1mM reduced glutathione, 20mg/ml gelatin and 0.001mM Hematin). Once diluted the enzyme solution was then sonicated for 5 seconds (Branson sonicator, setting 4, 1cm tip) to ensure a homogeneous suspension. 155µl enzyme solution was then added to each well of a 96-well microtitre plate containing either 5µl test compound (40x required test concentration) or 5µl DMSO for controls. Plates were then mixed and incubated at room temperature for 1 hour. Following the incubation period, 40µl of 0.5µM arachidonic acid was added to each well to give a final concentration of 0.1µM. Plates were then mixed and incubated for exactly 10 minutes (room temperature) prior to addition of 25µl 1M HCl (hydrochloric acid) to each well to stop the reaction. 25µl of 1M NaOH (sodium hydroxide) was then added to each well to neutralise the solution prior to determination of $PGE_2$ levels by enzyme immunoassay (EIA).

The following $IC_{50}$ values for inhibition of COX-2 and COX-1 were obtained from the microsomal assay for compounds of the invention:

| Example No. | COX-2: $IC_{50}$(nM) | COX-1: $IC_{50}$(nM) |
|---|---|---|
| 6 | <10 | 3,752 |
| 7 | <10 | 79,889 |
| 8 | <10 | 1,860 |
| 9 | 22 | 69,000 |
| 10 | 22 | >30000 |

## EXAMPLE 14
### Depression/anxiety study

Activity of the compounds (I), alone or in combination with antidepressants, vs. depression/anxiety may be evaluated according to the following models:

- Porsolt test in mose for SSRI/TCA (tricyclic antidepressants) (Porsolt et al 1977, Arch Int Pharmacodyn Ther,: 229, 327-336);
- Chronic mild stress in rat for SSRI/TCA (Willner, 1991, TiPS,: 12, 131-136);
- Maternal deprivation in rat pups for SSRI (or modulator of serotonin receptors)/TCA or CRF1 antag (Gardner, 1985, J. Pharmacol. Methods 14: 181-187);
- Rat social interaction after chronic treatment with SSRI (or modulator of serotonin receptors such as 5-HT2c antagonist)/TCA ( File, 1980 J. Neurosci Methods, 2:219-238; Lightowler et al., 1994, Pharmacol., Biochem. Behaviour,: 49, 281-285);
- Gerbil social interaction after chronic treatment with SSRI (or modulator of serotonin receptors)/TCA or NK1 antag (File, 1997, Pharmacol. Biochem. Behav. 58: 747-752);
- Human treat test in marmoset for NK1 or CRF1 antag (Costall et al. 1990, Pharmacol Biochem Behav,: 36: 13 ).

## EXAMPLE 15
### Patient study

In the following, the invention will be discussed in more detail with reference to a patient study. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. The results of the patient study are graphically represented in the attached figures, which will be discussed in more detail in the following.

The study may be performed as a multicenter, double-blind, placebo controlled randomised, parallel group determination of efficacy of compound 1-3 in combination with risperidone vs risperidone with placebo.

The patients may receive 2-6 mg/day of risperidone (Risperdal (E)), and, depending on which group they belonged, either 200 mg of 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine once daily or placebo over 12 weeks after a brief wash-out period of earlier antipsychotic medication.
During the wash-out period, a benzodiazepine preparation (mostly lorazepam) may be prescribed, if necessary. Patients with agitation, anxiety, or sleeping problems may be also medicated with lorazepam during the study.

Efficacy and tolerability of the compound 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine /risperidone *vs* placebo/risperidone will be assessed using the

following endpoints – positive and negative syndrome scale (PANSS), Clinical Global Impression score (CGI), AIMS, Simpson and Angus, Barnes Akathisia, Calgary Depression Scale and cognition endpoints.

The use of biperiden may be monitored as a possible indicator for side effects of the antipsychotic medication.

In order to exclude the chance that possible differences in the therapeutic effectiveness between the two groups might be due to non-compliance during the risperidone therapy or to differences in risperidone metabolism, the plasma levels of risperidone or 9-OH-risperidone may be monitored during the study.

The statistics may be performed according to the criterion of"last observation carried forward" (LOCF), i. e., the last PANSS scores of the patients who dropped out before the end of the study were carried forward to all subsequent observation days.
For the comparison of the main efficacy parameter, the mean change in the PANSS between the two treatment groups, t-tests for independent samples may be employed. With reference to the underlying hypothesis of a better outcome of the compound 1-3 risperidone group, a significance of $p < 0.05$ may be calculated in the one-tailed t-test and used as the basis for the estimation of the sample size (statistical power) and for the comparison of the groups. For all other comparisons, two-tailed t-tests may be used.

The improved effectiveness of the combination therapy with compound 1-3 /risperidone in comparison to risperidone monotherapy may be clearly shown by the significantly lower PANSS global scores after the 2,3,4 and 5 weeks of treatment.

Therefore, it could be excluded that the observed differences in the therapeutic effectiveness between the two groups may be due to incompatibility during the risperidone therapy or differences in risperidone metabolism.
The therapeutic benefit of the combined therapy may be attributed to the COX-2 inhibitor, compound 1-3.

The combination of compound 1-3 and risperidone according to the present invention may show improved results compared to the monopreparation risperidone with regard to effectiveness in the treatment of schizophrenia.
Furthermore, the use of compound 1-3 as adjunctive therapy may also be useful in the treatment of depressive states.

The combination of the COX-2 inhibitor as defined above and risperidone according to the present invention thus may show improved results compared to the monopreparation risperidone with regard to effectiveness in the treatment of schizophrenia.

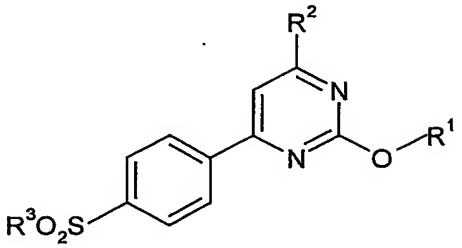
All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

It is to be understood that the present invention covers all combinations of particular and preferred groups described herein above.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

CLAIMS

1. Use of a COX-2 inhibitor of formula (I)



(I)

in which:

$R^1$ is selected from the group consisting of H, $C_{1-6}$alkyl, $C_{1-2}$alkyl substituted by one to five fluorine atoms, $C_{3-6}$alkenyl, $C_{3-6}$alkynyl, $C_{3-10}$cycloalkyl$C_{0-6}$alkyl, $C_{4-12}$bridged cycloalkyl, $A(CR^4R^5)_n$ and $B(CR^4R^5)_n$;

$R^2$ is $C_{1-2}$alkyl substituted by one to five fluorine atoms;

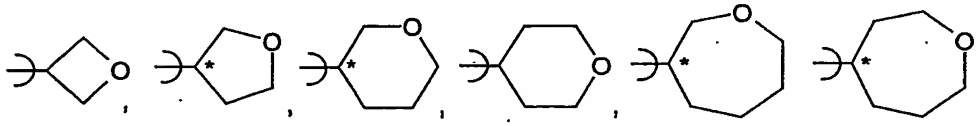
$R^3$ is selected from the group consisting of $C_{1-6}$alkyl, $NH_2$ and $R^7CONH$;

$R^4$ and $R^5$ are independently selected from H or $C_{1-6}$alkyl;

A is an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more $R^6$;

$R^6$ is selected from the group consisting of halogen, $C_{1-6}$alkyl, $C_{1-6}$alkyl substituted by one more fluorine atoms, $C_{1-6}$alkoxy, $C_{1-6}$alkoxy substituted by one or more F, $NH_2SO_2$ and $C_{1-6}$alkyl$SO_2$;

B is selected from the group consisting of



where ) defines the point of attachment of the ring;

$R^7$ is selected from the group consisting of H, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, $C_{1-6}$alkyl$OC_{1-6}$alkyl, phenyl, $HO_2CC_{1-6}$alkyl, $C_{1-6}$alkyl$OCOC_{1-6}$alkyl, $C_{1-6}$alkyl$OCO$, $H_2NC_{1-6}$alkyl, $C_{1-6}$alkyl$OCONHC_{1-6}$alkyl and $C_{1-6}$alkyl$CONHC_{1-6}$alkyl; and

n is 0 to 4;

in the preparation of a medicament for the treatment of psychiatric disorders.

2. Use of a COX-2 inhibitor of formula (I), as defined in claim 1, in combination with a neuroleptic drug or an antidepressant in the preparation of a medicament for the treatment of psychiatric disorders.

3. Use according to Claim 1 or 2 for the treatment of schizophrenia, delusional disorders, affective disorders, autism and tic disorders.

4. Use according to Claim 1 or 2 for the treatment of chronic schizophrenic psychoses, schizoaffective psychoses, temporary acute psychotic disorders, depressive episodes, recurring depressive episodes, manic episodes and bipolar affective disorders.

5. Use according to Claim 1 or 2 for the treatment of major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders

6. Use according to anyone of Claims 1 to 5, characterised in that the COX-2 inhibitor is selected from :
2-(4-fluorophenoxy)-4-[4-(methylsulfonyl)phenyl]-6](trifluoromethyl)pyrimidine;
2-(4-methoxyphenoxy)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl)pyrimidine;
2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine;
2-[(5-chloropyridin-3-yl)oxy]-4-[4-(methylsulfony)phenyl]-6-(trifluoromethyl)-pyrimidine;
2-(cyclohexyloxy)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine.

7. Use according to Claim 6, characterized in that 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine or a pharmaceutical acceptable salt thereof is used as COX-2 inhibitor.

8. Use according to anyone of Claims 1 to 7, characterised in that the neuroleptic is selected from clozapine, olanzapine, ziprasidone, risperidone, aripiprazole, quetiapine, quetiapine fumarate, sertindole, amisulpride, haloperidol, haloperidol decanoate, haloperidol lactate, chlorpromazine, fluphenazine, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride, thiothixene, thiothixene hydrochloride, trifluoperazine, perphenazine, amitriptyline, thioridazine, mesoridazine, molindone, molindone hydrochloride, loxapine, loxapine hydrochloride, loxapine succinate, pimozide, flupenthixol, promazine, triflupromazine, chlorprothixene, droperidol, actophenazine, prochlorperazine, methotrimeprazine, pipotiazine, ziprasidone, hoperidone, zuclopenthixol, and mixtures thereof.

9. Use according to anyone of Claims 1 to 8, characterised in that the antidepressant is selected from amitriptyline, amitriptyline oxide, desipramine, dibenzepin, dosulepin, doxepin, chloroimipramine, imipramine, nortriptyline, mianserin,

maprotiline, trimipramine, viloxazine, trazodone, nefazodone, mirtazapine, venlafaxine, reboxetine, tranylcypromine, brofaromine, moclobemide, citalopram, paroxetine, fluoxetine, fluvoxamine, sertraline, Hypericum (St. John's Wort), and mixtures thereof.

10. Use according to Claim 9, characterised in that risperidone or aripiprazole is used as a neuroleptic.

11. Use according to Claim 7 and 10, characterised in that 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine or a pharmaceutical acceptable salt thereof and risperidone are administered in an amount of 0.8-3.0 mg/kg and 2-6 mg, respectively.

12. Use according to Claim 11, characterised in that 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine or a pharmaceutical acceptable salt thereof and risperidone are administered in an amount of 200 mg and 4-5 mg, respectively.

13. Use according to anyone of Claims 1 to 12, characterised in that the medicament is administered orally.

14. Use according to anyone of the preceding Claims, characterised in that a tranquilliser, preferably lorazepam, is administered additionally.

15. Kit-of-parts suitable for use in the treatment of psychiatric disorders, comprising a first dosage form comprising a neuroleptic drug or an antidepressant and a second dosage form comprising a COX-2 inhibitor as defined in claim 1 or prodrug thereof, for simultaneous, separate or sequential administration.

16. Kit-of-parts according to Claim 15, characterised in that the neuroleptic is selected from clozapine, olanzapine, ziprasidone, risperidone, quetiapine, quetiapine fumarate, sertindole, amisulpride, haloperidol, haloperidol decanoate, haloperidol lactate, chlorpromazine, fluphenazine, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride, thiothixene, thiothixene hydrochloride, trifluoperazine, perphenazine, amitriptyline, thioridazine, mesoridazine, molindone, molindone hydrochloride, loxapine, loxapine hydrochloride, loxapine succinate, pimozide, flupenthixol, promazine, triflupromazine, chlorprothixene, droperidol, actophenazine, prochlorperazine, methotrimeprazine, pipotiazine, ziprasidone, hoperidone, zuclopenthixol, and mixtures thereof.

17. Kit-of-parts according to Claim 16, characterized in that the antidepressant is selected from amitriptyline, amitriptyline oxide, desipramine, dibenzepin, dosulepin, doxepin, chloroimipramine, imipramine, nortriptyline, mianserin, maprotiline,

trimipramine, viloxazine, trazodone, nefazodone, mirtazapine, venlafaxine, reboxetine, tranylcypromine, brofaromine, moclobemide, citalopram, paroxetine, fluoxetine, fluvoxamine, sertraline, Hypericum (St. John's Wort), and mixtures thereof.

18. Kit-of-parts according to anyone of Claims 15 to 17, characterized in that the COX-2 inhibitor is selected from one of the compound of claim 1 in mixture with another COX-2 inhibitor selected in the group from; celecoxib, rofecoxib, meloxicam, piroxicam, deracoxib, parecoxib, valdecoxib, etoricoxib, a chromene derivative, a chroman derivative, N- (2-cyclohexyloxynitrophenyl) methyl sulfonamide, COX189, ABT963 or JTE-522, pharmaceutical acceptable salts, or prodrugs thereof.

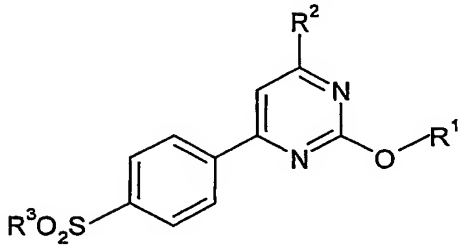
19. Kit-of-parts according to anyone of Claims 15, 16 or 17, characterized by comprising 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine or a pharmaceutical acceptable salt thereof as COX-2 inhibitor and risperidone as neuroleptic drug.

20. Kit-of-parts according to Claim 19, characterized by comprising 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine or a pharmaceutical acceptable salt thereof and risperidone in an amount of 0.8-3.0 mg/kg mg and 2-6 mg, respectively.

21. A method for treatment and/or prophylaxis of psychiatric disorders, as defined in claims 3, 4, and 5, in a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a kit–of-parts as claimed in any of claims 15 to 20.

ABSTRACT

The invention concerns the use of pyrimidine derivatives of formula I



(I)

which are COX-2 (cyclooxygenase-2) inhibitors, for the treatment of psychiatric disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychoses and schizoaffective psychoses, temporary acute psychotic disorders; or in the treatment or prevention of major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders. Moreover, the invention is concerned with the use of a pyrimidine derivative known as COX-2 inhibitor in combination with a neuroleptic drug or an antidepressant for the treatment of psychiatric disorders such as those defined above.